REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative at 858 720 5133.

Status of the Claims

Pending claims

Claims 1, 4, 12, 16, 19, 20, 22 and 23 are pending.

Claims added in the instant amendment

Claims 24 to 45 are added. Thus, after entry of the instant amendment, claims 1, 4, 12, 16, 19, 20, 22 and 23 to 45 will be pending.

Outstanding Rejections

Claims 4, 12, 14, 16 and 18 to 23 stand rejected under 35 U.S.C. §112, first and second paragraphs. Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims. For example, support for claims directed to use of dominant negative phospholamban (PLB) in the treatment of heart failure can be found, inter alia, in the paragraph spanning pages 6 and 7, where the specification describes use of an exemplary dominant negative PLB that can bind to PLB to imitate phosphorylation of PLB, i.e., to attenuate the inhibition of SERCA2a. See also the section entitled "Peptide based therapeutic for inhibition of PLB activity" on pages 22 to 25, discussing how PLB function can be inhibited in a dominant negative manner. In the paragraph spanning pages 18 and 19, it is noted that this exemplary dominant negative PLB interacts with endogenous, or "wild-type" PLB. Specification also discusses, inter alia, on pages 21 to 22, and shows data, that the exemplary dominant negative PLB of the invention is effective in changing myocyte contractility and relaxation. Examples 1 and 2 of the specification, pages 25 to 27, describe exemplary methods to determine if a

composition (e.g., a dominant negative polypeptide) is effective in modifying myocyte and cardiac function. Support for claims directed to methods for the treatment of heart failure by administering a dominant negative phospholamban (PLB) linked to a transport peptide, such as an antennapedia transport peptide, by a linker, e.g., polylysine, to a cardiomyocyte to enhance contractility of the cell can be found, inter alia, in Example 4, pages 28 to 29. Support for methods wherein the antennapedia transport peptide comprises SEQ ID NO:7 or the exogenous dominant negative PLB protein comprises the first 16 residues of SEQ ID NO:8 can also be found, inter alia, in Example 4.

Information Disclosure Statements

Applicants thank the Examiner for expressly considering (and initialing) the Information Disclosure Statements (IDSs) and Forms PTO-1449, submitted September 23, 2003.

A new IDS and Forms PTO-1449 are enclosed with this response. Copies of the references are enclosed. It is respectfully requested that the cited information be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

Issues under 35 U.S.C. §112, first paragraph

Enablement

Claims 4 to 6, 7 to 11 and 12 to 17 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention (please see page 2, line 18, to page 7, of the instant office action).

The Patent Office states that the specification is enabling for gene-mediated ablation of endogenous PLB in a double-knockout mouse to enhance cardiac contractility.

However, it is alleged, inter alia, that the specification does not provide reasonable enablement for application or administration of an exogenous dominant negative PLB protein, PLB mutant or truncated PLB in order to induce PLB deficiency. It is also alleged that, unlike gene-mediated transfection of cells, there is no constant production of the protein in the cells and therefore it is not readily apparent that sufficient protein can be administered *in vivo* or

in vitro to provide the functionality as claimed (see, for example, the last full sentence of page 4 of the office action).

The specification presents data that demonstrates that exogenous PLB can be used to enhance cardiac contractility by live myocytes. The specification enables methods of the invention directed to gene-mediated enhancement of cardiac contractility by inhibition of endogenous PLB activity by an exogenous dominant negative PLB. This is demonstrated using an art-accepted animal model. For example, please note Example 3, pages 27 to 28, where the specification provides data demonstrating that mutant human PLB expressed intracellularly by *in vivo* gene transfer effectively shorted mouse cardiac cells. Also, please note Example 2 and Figure 3, where the specification provides data demonstrating that lack of PLB (using a knockout mouse model) significantly affected intracellular calcium concentrations. Also, please note Example 1, where the specification describes the results of data demonstrating that lack of PLB (using a knockout mouse model) results in the equivalent of heart failure.

As noted above, it is alleged that the specification does not provide reasonable enablement for application or administration of an exogenous dominant negative PLB protein, PLB mutant or truncated PLB in order to induce PLB deficiency. Thus, the issue is not whether once inside a cell an exogenous PLB can inhibit endogenous PLB activity to enhance cardiac contractility or treat heart failure, but, whether the specification enables one of skill how to apply or administer an exogenous PLB to successfully practice the methods of the invention.

Applicants respectfully aver that the specification enables methods of the invention directed to administration of exogenous mutated PLB protein to inhibit endogenous wild-type PLB activity and enhance cardiac contractility. As declared by Dr. Chien (please see attached Rule 132 declaration), the specification presents data that demonstrates that PLB inhibitor molecule linked (using e.g., polylysine) to a transport peptide (e.g., antennapedia transport peptide) can induce enhanced contractility in a cardiac cell. For example, Example 4, pages 28 to 29, provides data that demonstrates that a mutant PLB molecule linked to a transport molecule via a polylysine was efficiently translocated into isolated rat cardiomyocytes. These cardiomyocytes showed enhanced contractility. The results of these experiments are illustrated in Figures 5a and 5b.

Example 5, including Table 3, pages 20 to 31, describes experiments that administer a mutant PLB linked to a transport peptide to mouse cardiomyocytes. Table 3 summarizes data from those experiments. The Patent Office cites Example 5 to evidence its allegation of lack of enablement. As noted on page 31, lines 9 to 11, of Example 5, while there appeared to be a trend towards a larger, faster contraction in the myocyte, T-test analysis did not identify any statistical difference due to the high variability of the data. However, as declared by Dr. Chien, while the results of Example 5's experiments were inconclusive, the totality of the experimental evidence described in this specification (some of which is discussed and summarized, above) overwhelming and conclusively demonstrate that exogenous mutant PLB can inhibit the activity of endogenous PBL to improve cardiac contractility. Dr. Chien further notes that knowledge accrued since the filing of the specification confirms that exogenous mutant PLB can inhibit the activity endogenous PBL to improve cardiac contractility.

Furthermore, the specification enables one of skill how to apply or administer an exogenous PLB protein to successfully practice the methods of the invention. As discussed above, the specification teaches (e.g., in Example 4) that mutant PLB molecule linked to a transport molecule via a polylysine can be translocated into rat cardiomyocytes, resulting in these cardiomyocytes showing enhanced contractility. As declared by Dr. Chien, the level of skill in this art at the time of the invention was very high. As declared by Dr. Chien, using the teaching of the specification, one skilled in the art could have selected routine screening protocols known in the art at the time of the invention to determine means to effectively apply and administer exogenous PLB as claimed. Dr. Chien declares that using the teaching of the specification, one of skill in the art could have determined protocols to apply and administer an exogenous PLB protein linked to a transport protein to successfully practice the claimed methods of the invention.

The Patent Office correctly notes that it is the specification, not one of skill in the art, that must supply the novel aspects of the invention in order to constitute adequate enablement (see lines 15 to 17, page 6 of the office action). However, the novel aspects of the methods of the invention, including exemplary compounds used to practice the methods of the invention, are described and enabled by the specification. As declared by Dr. Chien, selecting

protocols to effectively apply and administer exogenous PLB protein as claimed could have been determined by the skilled artisan using routine screening.

Whether large numbers of compositions (e.g., enzymes, antibodies, nucleic acids, and the like) must be screened to determine if one is within the scope of the claimed invention is irrelevant to an enablement inquiry. Enablement is not precluded by the necessity to screen large numbers of compositions, as long as that screening is "routine," i.e., not "undue," to use the words of the Federal Circuit. The Federal Circuit in In re Wands directed that the focus of the enablement inquiry should be whether the experimentation needed to practice the invention is or is not "undue" experimentation. The court set forth specific factors to be considered.

One of these factors is "the quantity of experimentation necessary." Guidance as to how much experimentation may be needed and still not be "undue" was set forth by the Federal Circuit in, e.g. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). In Hybritech, Inc., a single deposited antibody producing cell line enabled a claim generic to all IgM antibodies directed to a specific antigen. The Federal Circuit noted that the evidence indicated that those skilled in the monoclonal antibody art could, using the state of the art and applicants' written disclosure, produce and screen new hybridomas secreting other monoclonal antibodies falling within the genus without undue experimentation. The court held that applicants' claims need not be limited to the specific, single antibody secreted by the deposited hybridoma cell line (significantly, the genus of antibodies was allowed even though only one antibody specie was disclosed). The court was acknowledging that, because practitioners in that art are prepared to screen large numbers of negatives in order to find a sample that has the desired properties, the screening that would be necessary to make additional antibody species was not "undue experimentation."

Analogously, practitioners of the medical sciences for the instant invention also recognized the need to screen numbers of negatives to find a sample that has the desired properties, for example, determining protocols to effectively apply and administer exogenous PLB protein as claimed. As declared by Dr. Chien, the screening procedures used to identify protocols to effectively apply and administer exogenous PLB protein were all well known in the art and at the time this application was filed. All were routine protocols for the skilled artisan.

Thus, the skilled artisan using Applicants' written disclosure could practice the instant claimed invention without undue experimentation.

Accordingly, Applicants respectfully submit that the pending claims meet the enablement requirements under 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully submit that amended claims are fully enabled by and described in the specification to overcome the rejection based upon 35 U.S.C. §112, first paragraph.

Issues under 35 U.S.C. §112, second paragraph

Claims 4, 12, 14, 16 and 18 to 23 stand rejected under 35 U.S.C. §112, second paragraph, for allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention (please see the section spanning pages 7 and 8 of the office action). The instant amendment addresses this issue.

Issues under 35 U.S.C. §112, first paragraph

Written Description

Claims 1, 4, 12, 16, 19, 20, 22 and 23 are newly rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention (please see page 8 of the office action). This is a new matter rejection.

In particular, the Patent Office alleged, inter alia, that exogenous dominant negative phospholambans (PLBs) are not described in the specification. However, an exemplary dominant negative PLB is described, inter alia, in Example 4, page 28, lines 24 to 26, as a cargo peptide derived from the first 16 residues of PLB, or, SEQ ID NO:8. The specification also notes (page 28, lines 26 to 28), and as declared by Dr. Chien, additional cargo sequences could also have been derived from any segment of wild-type PLB or mutant PLB. As declared by Dr. Chien, determining additional dominant negative PLB species could have been determined by the skilled artisan using routine screening methods, including the exemplary methods described in the specification.

Accordingly, Applicants respectfully submit that the pending claims meet the written description requirement under 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully submit that amended claims are fully enabled by and described in the specification to overcome the rejection based upon 35 U.S.C. §112, first paragraph.

Issues under 35 U.S.C. §112, second paragraph

Claims 4, 12, 141, 16 and 18 to 23 stand newly rejected under 35 U.S.C. §112, second paragraph, for allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention (please see page 9 of the office action).

The Patent Office is also concerned that the term "dominant negative" is unclear. To address this issue, Dr. Chien declares that the term "dominant negative" was well known in the art at the time of the invention and the specification uses the term as it would have been understood to one skilled in the art at the time of the invention. Dr. Chien, an expert in the art at the time of the invention, declares that an example of a textbook definition for "dominant negative protein" now, and at the time of the invention (the definition has not changed) is "a mutant protein that as a result of the mutation has lost activity or function and interferes with the function of its corresponding wild-type protein." Applicants note that the specification, including the claims, use the term as it would have been understood to one skilled in the art at the time of the invention (and now, as the definition has not changed). Thus, at the time of the invention, and now, the skilled artisan would have understood that a "dominant negative protein" is a mutant protein that as a result of the mutation has lost activity or function and the mutant protein interferes with the function of its corresponding wild-type protein.

Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. §112, second paragraph, can be properly withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs. Applicants respectfully submit that all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicants believe that no additional fees are necessitated by the present response and amendment. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 06-1050. Please credit any overpayment to this account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at 858 720 5133.

Respectfully submitted,

Date: May 20, 2004

Gregory P. Einhorn
Reg. No. 38,440

Morrison & Foerster LLP
3811 Valley Centre Drive
San Diego CA 92130-2332
Tel: 858 720